REMARKS

Entry of the foregoing, reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

Claims 44, 46, 48-49, 55, 62, 64-65, 69, 71-75, 79, and 80 are pending. Claims 64 and 71 are cancelled herein without prejudice or disclaimer thereto. Claims 44, 48, 65 and 74 are amended herein. Basis for the amendments may be found through the specification and claims as-filed, especially at page 11, lines 26-29, Example V, and in claims 64 and 71 as filed.

Rejections Under 35 U.S.C. §103

Claims 44, 46, 48, 55, 56, 62, and 64 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Lowy et al. (U.S. Patent No. 5,618,536) ("Lowy"), Hagensee et al. (1993, *J. Virol.* 67:315-322) ("Hagensee"), Borysiewicz et al. (June 1996, *Lancet* 347:1523-1527) ("Borysiewicz), Galloway (1994, *Infectious Agent and Disease* 3: 187-193) ("Galloway"), Meyer et al. (1991, *J. Gen. Virol.* 72: 1031-1038) ("Meyer "), Boursnell et al. (U.S. Patent No. 5,719,054) ("Boursnell"), Bubenik et al. (*International Journal of Oncology* 1996, 8:447-481) ("Bubenik"), Bash et al. (1993, *J. Immunol.* 14:269-272) and Sutter et al. (U.S. Patent No. 6,440,422) ("Sutter").

In order to establish a case of *prima facie* obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation to modify the reference or combine reference teachings, (2) there must be a reasonable expectation of success, and (3) the prior art reference(s) must teach or suggest all of the claim limitations. *See* M.P.E.P. §2142. Applicants respectfully submit that these criteria have not been met in the present Office Action, as the cited references, alone or in combination, fail to recite all of the elements of the presently claimed invention or to provide an expectation of success or motivation to arrive at the claimed invention, especially as amended herein.

In the interest of expediting prosecution, claim 44 is amended herein to recite that the composition consists of a MVA vector, into which the DNA sequences are inserted within excisions II and/or III. Claim 48 is amended to recite the sequences as seen in Example V, and thus is directed to a composition, wherein the DNA

sequence coding for the E6 polypeptide of a papillomavirus, the DNA sequence coding for the E7 polypeptide of a papillomavirus and the DNA sequence coding for interleukin-2 are inserted within excision III of the recombinant vector, and wherein the DNA sequence coding for the L1 polypeptide of a papillomavirus and the DNA sequence coding for the L2 polypeptide of a papillomavirus are inserted within excision III of the recombinant vector.

Similarly, claim 65 is amended to recite that the composition consists of a MVA vector, into which the DNA sequences are inserted with excisions II and/or III. Claim 74 is amended to recite that the recited DNA sequences are inserted within excision III of the MVA recombinant vector.

Attached herewith is a Declaration under 37 C.F.R. § 1.131 executed by Jean-Marc Balloul. Jean-Marc Balloul states that the invention was conceived prior to March 1996, and that conception was pursued with diligence from the time it was conceived before March 1996 at least until the filing of the priority application, French Application No. 96-09584, on July 30, 1996. In support of the Declaration, an internal report from prior to March 1996 is provided as Exhibit A, which discusses the production of clinical batches of vaccina virus construct VVTG5021 & 5065, as well as expression of HPV genes and IL-2 and the absence of toxicity seen in animal models following injection.

Thus, Applicants submit that any cited references from the Office Action which are dated March 1996 or after should be removed as citable references. Borysiewicz et al. (*Lancet* 347:1523-1527) is dated June 1996; Bubenik et al. (*International Journal of Oncology*, 8:447-481) is dated March 1996 (as noted by the Office on the face of the reference as provided), and Sutter et al. (U.S. Patent No. 6,440,422) is dated June 3, 1996 for purposes of the U.S. filing date. Thus, Applicants request that these three references be removed.

Though Applicants submit that Bubenik, Borysiewicz, and Sutter should be removed as cited references, Applicants address all of the references as cited, on the merits for completeness. The Office asserts that one of ordinary skill in the art at the time the invention was made would have been motivated to express the four therapeutic and protective papillomavirus genes of Galloway, Lowy, Boursnell, Borysiewicz and Hagenesee and the IL-2 of Bubenik and Bash in the MVA vaccinia vector of Meyer and Sutter. The Office states that in view of Sutter, one of ordinary

skill in the art would have recognized that expression of multiple heterologous genes could have been successfully accomplished in an MVA vector. Applicants disagree, and submit that the cited references do not disclose or suggest the present claims, especially as amended herein. As amended herein, the present invention is now directed to a composition consisting of a MVA vector with the five recited DNA sequences inserted within excision II and/or III. Excision III is not cited as potential insertion site in Sutter.

The newly cited reference, Bash, does not remedy to the deficiencies of the other references. Bash describes a recombinant vaccinia virus vector containing and expressing the IL-2 gene. Morphologic modifications of tumor appearance are observed following intratumor injection of the IL-2-expressing vaccinia as evidenced by tumor shrinkage and two or three regression. Bash does not disclose or suggest a vector containing and expressing HPV antigens further to IL-2.

The skilled artisan would have no expectation of success in constructing a MVA vector having a total of five foreign gene sequences, *i.e.,* the four papillomavirus early and late genes, and the IL-2 gene, each expressed from independent expression elements and inserted in one or two excision sites of the MVA genome.

Expression of multiple foreign gene sequences is not a straightforward matter. Prior art references disclose expression of a maximum of <u>two</u> expression cassettes in a single vaccinia vector.

Applicants submit that the skilled artisan would have no expectation of success in constructing a MVA vector having three foreign gene sequences, *i.e.,* the early papillomavirus E6 and E7 genes, and the IL-2 gene, each expressed from independent expression elements and inserted in excision III of the MVA genome.

On page 5, the Office Action refers to claims 16 and 24 of Sutter, stating that "Sutter et al. explicitly claim an MVA vector expressing five heterologous genes under the control of separate promoters" and further that "Sutter et al. explicitly claim expressing five heterologous genes from five of the deletion sites of MVA". Applicants disagree with this interpretation of Sutter. Claim 16 of Sutter (U.S. Patent No. 6,440,422) recites:

16. A recombinant Modified Vaccinia Ankara (MVA) virus containing and capable of expressing at least one foreign gene inserted at a site of a naturally

occurring deletion within the MVA genome, wherein the site of the naturally occurring deletion is selected from the group consisting of site I, site II, site IV, site V and site VI. Claim 24 reads:

24. The recombinant Modified Vaccinia Ankara (MVA) virus according to claim 16 wherein the foreign gene is under transcriptional control of the vaccinia virus early/late promoter P7.5.

Claim 16 of Sutter is thus directed to a recombinant MVA vector comprising and capable of expressing at least one foreign gene. The foreign genes are inserted within the viral genome at a naturally-occurring deletion site, *i.e.,* deletion I, deletion II deletion IV, deletion V or deletion VI. Claim 24 is directed to the recombinant MVA vector of claim 16, and thus has at least one foreign gene inserted within the viral genome at a site of a naturally-occurring deletion. Claim 24 states that the foreign gene is placed under the control of the vaccinia 7.5 promoter.

These claims cover insertion of at least one foreign gene in any of the five naturally-occurring deletion sites. However, claims 16 and 24 of Sutter are not directed to a recombinant MVA vector comprising five foreign genes inserted in the five naturally-occurring deletion sites. The embodiments exemplified in Sutter support this interpretation, as they are directed to recombinant MVA vectors comprising a maximum of two foreign genes inserted into the naturally-occurring deletion II (see Figures 4-6). Thus, when reviewing Sutter as a whole, it is not the case that "Sutter et al. explicitly claim an MVA vector expressing five heterologous genes under the control of separate promoters".

Applicants also refer to column 9 lines 5-22 of Sutter, which discusses the use of the recombinant T7-expressing MVA vector in combination with a foreign gene encoding an antigen of interest. Sutter does not view insertion of the antigen-coding gene into the T7 recombinant MVA vector, but rather proposes insertion of the antigen-coding gene in an independent vector which will be inoculated simultaneously or with appropriate limelags together with the MVA vector.

Thus, the fact that MVA contains six deletions (I to VI) which are potential insertion sites for foreign genes does not address the problem in the art of expressing multiple genes, as compared to a vaccinia vector. First, some potential insertion sites are available in the vaccinia genome, such as K1L and TK genes identified in the present application (page 11 lines 21-23) as well as sites A-D

identified in Boursnell column 12 lines 25-31). Moreover, gene expression is not merely a matter of identifying appropriate insertion sites within a viral genome. Expression of a gene is a complex matter involving transcriptional as well as translational regulatory elements to have the DNA properly transcribed in mRNA and the mRNA properly translated in protein. Co-expression of multiple gene sequences is even trickier due to the interferences that may occur between the various transcriptional and translational regulatory elements used for expressing each gene.

This is confirmed by Boursnell, which recognizes that expression of four gene sequences from independent promoters can be difficult to achieve in a vaccinia virus vector (see column 9 lines 64-67 and column 10, line 1 of Boursnell). MVA is part of the vaccinia virus genus, and the teaching of Boursnell is relevant to the skilled artisan's views on expression in MVA vector. Boursnell discloses the expression of fusion proteins in order to overcome the technical problem of multiple gene expression, so as to remain with two expression units in the vaccinia genome, rather than four. Applicants request that this rejection be withdrawn.

Claim 49 remains rejected under 35 U.S.C. §103(a) as purportedly being unpatentable over the documents in the rejection above and further in view of Crook et al. (1991, Cell 67: 547-556) ("Crook") and Munger et al. (1989, EMBO 8: 4099-41 05) ("Munger"). Applicants submit that claim 49 depends upon claim 44. Crook and Munger do not remedy the deficiencies of the previously cited references over claim 44, especially as amended herein.

Claims 65, 69, 71, 72, 74, 79 and 80 stand rejected under 35 U.S.C. §103(a) as purportedly unpatentable over Borysiewicz, Meyer, Boursnell, Bubenik, Bash and Sutter. As previously discussed above, the expression of multiple foreign gene sequences is not straightforward, and the cited references merely disclose a maximum of two expression cassettes in a single vaccinia vector. Thus, the skilled artisan would not have an expectation of success in preparing a MVA vector having three foreign gene sequences (the early papillomavirus E6 and E7 genes, as well as the IL-2 gene) that is each expressed from independent expression elements and inserted into excision III of the MVA genome, as recited in amended claim 65.

In light of the above comments, Applicants request that this rejection be withdrawn.

Claim 75 remains rejected under 35 U.S.C. §103(a) as purportedly being unpatentable over the same documents as applied above to claims 65, 69, 71, 72, 74, 79 and 80 and further in view of Crook and Munger. Claim 75 is a dependent claim referring back to claim 65. Crook and Munger do not remedy the deficiencies in the rejections against claim 65.

In light of the above, Applicants request that the rejections under 35 U.S.C. § 103 should be withdrawn.

CONCLUSION

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this Amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (703) 836-6620 so that prosecution of the application may be expedited.

Respectfully submitted,

BUCHANAN INGERSOLL PC

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Enclosure: Declaration by Jean-Marc Balloul under 37 C.F.R. §1.131
Exhibit A